Clinical Case Report

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Effectiveness of the traditional Japanese Kampo medicine Yokukansan for chronic migraine

A case report

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Abstract

Rationale: The traditional Japanese Kampo medicine Yokukansan (TSUMURA Yokukansan extract granules) was originally used to treat neurosis, insomnia, night crying, and irritability and/or agitation in infants and recently it has also been used for neuropsychiatric symptoms in Alzheimer's disease or other dementia in Japan. Furthermore, several recent studies have reported the efficacy of Kampo medicines for various types of headache. Here, we report a case of severe chronic migraine refractory to prophylactic therapy using various western medicines and Japanese Kampo medicines that had resulted in a leave of absence from work, but for which the frequency and severity were markedly decreased by Yokukansan (2.5 g 3 times/d), enabling the patient to return to work fully.

Patient concerns: The patient was a 39-year-old woman with a diagnosis of migraine without aura, which started around the age of 17 years and had been well managed with oral triptan preparations. However, due to lifestyle changes after childbirth, the frequency and severity of migraine increased at 38 years of age, prompting her to visit our hospital.

Diagnoses: Our initial examination found no neurological abnormality, and our diagnosis was also migraine without aura based on the International Classification of Headache Disorders version 3.

Interventions: Her migraine had become refractory to several western medicines (lomerizine hydrochloride, propranolol, sodium valproate, amitriptyline, and duloxetine) and 2 Japanese Kampo medicines (Goshuyuto and Chotosan). The migraine episodes worsened, and consequently she took a leave of absence from work.

Outcomes: Yokukansan was then tried, and this markedly improved the chronic migraine, enabling her full return to work.

Lessons: Yokukansan might have exerted a prophylactic effect on chronic migraine via its action on the glutamatergic and serotonergic systems, inhibitory action on orexin A secretion, and anti-inflammatory action. Yokukansan might be useful as a prophylactic for migraine worldwide, and a future large-scale clinical study is warranted.

Abbreviations: ICHD-3 = International Classification of Headache Disorders version 3, OTC = over-the-counter.

Keywords: chronic migraine, leave of absence, traditional Japanese Kampo medicine, Yokukansan

1. Introduction

The efficacy of traditional Japanese Kampo medicines for a number of conditions such as headache has been reported in recent years. The Clinical Practice Guidelines for Chronic Headache published by the Japanese Headache Society recommend (grade B) the use of the following 5 types of traditional Japanese Kampo medicines for migraine: Goshuyuto (evodia decoction), Keishininjinto (cinnamon twig and ginseng decoction), Chotosan (uncaria decoction), Kakkonto (kudzu decoction), and Goreisan (5-ingredient powder with poria).[1] The efficacy of other traditional Japanese Kampo medicines not mentioned in these guidelines has also been shown for various types of headache in several studies.[2–7] Although not commonly used for headache, the traditional Japanese Kampo medicine Yokukansan (TSUMURA Yokukansan extract granules; Tsumura Co Ltd, Tokyo, Japan; Fig. 1) has been reported for various types of headache.[8–14] Derived from the extracts of 7 medicinal herbs, Yokukansan was originally used to treat neurosis, insomnia, night crying, and irritability and/or agitation in infants and is an approved prescription drug in Japan. Recently, there have been several randomized controlled trials and a randomized double-blind placebo-controlled multicenter trial of Yokukansan for neuropsychiatric symptoms in Alzheimer's Disease or other dementia.[15]

Editor: N/A.

The Bioethics Committee of St. Marianna University School of Medicine provided a waiver for case presentation.

Written informed consent for publication was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

Results of 3-dimensional high-performance liquid chromatographic fingerprint analysis and the pictures of Yokukansan (TSUMURA Yokukansan extract granules) were provided by Tsumura Co. Ltd. Tokyo, Japan.

The authors have no conflicts of interest to disclose.

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A

B

C

Composition	7.5 g of TSUMURA Yokukansan extract granules (hereafter TJ-54) contains 3.25 g of a dried extract of the following mixed crude drugs.	
	JP Atractylodes Lancea Rhizome ..... 4.0 g	
	JP Poria Sclerotium ..... 4.0 g	
	JP Cnidium Rhizome ..... 3.0 g	
	JP Uncaria Hook ..... 3.0 g	
	JP Japanese Angelica Root ..... 3.0 g	
	JP Bupleurum Root ..... 2.0 g	
	JP Glycyrrhiza ..... 1.5 g	
	(JP: The Japanese Pharmacopoeia)	
	Inactive ingredients	JP Magnesium Stearate JP Lactose Hydrate
Description	Dosage form	Granules
	Color	Light grayish-brown
	Smell	Characteristic smell
	Taste	Slightly sweet and astringent
	ID code	TSUMURA/54

D

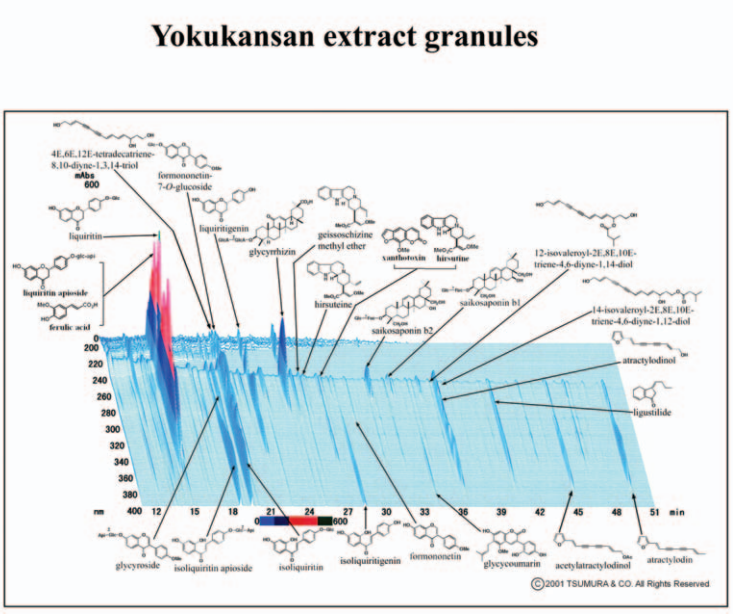

Figure 1. TSUMURA Yokukansan extract granules (A: appearance, B: extract granules, C: composition, D: 3D HPLC pattern). Yokukansan in granular form is a galenical preparation containing: Atractylodes lancea rhizome (4.0 g), Poria sclerotium (4.0 g), Cnidium rhizome (3.0 g), Uncaria hook (3.0 g), Japanese Angelica root (3.0 g), Bupleurum root (2.0 g), and Glycyrrhiza (1.5 g). 3D HPLC = 3-dimensional high-performance liquid chromatographic fingerprint.

Here, we report a remarkable case of chronic migraine that had resulted in a leave of absence from work due to refractoriness to prophylactic therapy using various kinds of established western medicines and traditional Japanese Kampo medicines as anti-migraine prophylactic agents. However, the frequency and severity of migraine episodes were markedly decreased by the addition of Yokukansan, enabling the patient to return to work fully.

2. Case presentation

A female company employee aged 39 years presented to the outpatient clinic in our university hospital in August 2017 with a chief complaint of chronic headache. There was no notable past medical history except for throbbing right frontal headaches without aura that had been occurring 1 or 2 times per month since she was 17 years old, and lasted for half a day for a period of 1 to 3 days once begun. Headaches caused her to avoid routine physical activity and were associated with visual, auditory, and olfactory hypersensitivity, but were relieved approximately 30 minutes after oral administration of 1 tablet (precise dose unknown) of an over-the-counter (OTC) acetylsalicylic acid preparation.

At age 37 years, 4 months after childbirth, she noticed an increases in the frequency of headaches to 2 or 3 times per month, which coincided with the return of menstruation while reducing the frequency of breastfeeding. The severity of headaches has also increased, with associated nausea but no vomiting. OTC acetylsalicylic acid had become ineffective, and she had to lie down during each episode. She visited a nearby neurosurgery outpatient clinic and was diagnosed as having migraine without aura and tension-type headache based on past medical history. Oral sumatriptan (1 tablet, 50 mg) and self-administered sumatriptan subcutaneous injection (3 mg) were prescribed for pain relief and were effective.

She returned to work after maternity leave at the age of 38 years and had been busy balancing work and childrearing. However, due to lifestyle changes after childbirth, the frequency and severity of migraine increased at 38 years of age. A tablet or 1 shot of sumatriptan became ineffective. So, she visited the neurosurgery outpatient clinic again, and multi-agent anti-migraine prophylactic therapy was started with sodium valproate (600 mg/d), lomerizine hydrochloride (10 mg/d), and amitriptyline (30 mg/d). However, this therapy caused drowsiness and severely affected her ability to work. Subsequently, she visited our university hospital in July in the same year at the age 39 years.

Our initial examination found no neurological abnormality, and our diagnosis was also migraine without aura based on the International Classification of Headache Disorders version 3 (ICHD-3). We replaced the previously prescribed self-administered sumatriptan with sumatriptan nasal spray (20 mg), because the injection caused discomfort immediately after administration. Two prophylactics (lomerizine hydrochloride, and amitriptyline) were discontinued, and only sodium valproate (600 mg/d) was continued on an outpatient basis (Fig. 2). The effects of both intranasal sumatriptan and newly prescribed oral naratriptan hydrochloride (1 tablet, 2.5 mg) were inadequate. The most effective pain relief was early administration of 2 tablets of sumatriptan (100 mg). However, migraines still occurred 12 to 14 times per month, and the dose of prophylactic sodium valproate was increased to 800 mg/d in November and to 1000 mg/d in December 2017. Migraine frequency remained high in February 2018, and amitriptyline (20 mg/d) was added to replace sodium valproate. However, because of the ensuing drowsiness, she stopped taking the amitriptyline after 3 days and switched it to leftover sodium valproate (1000 mg/d).

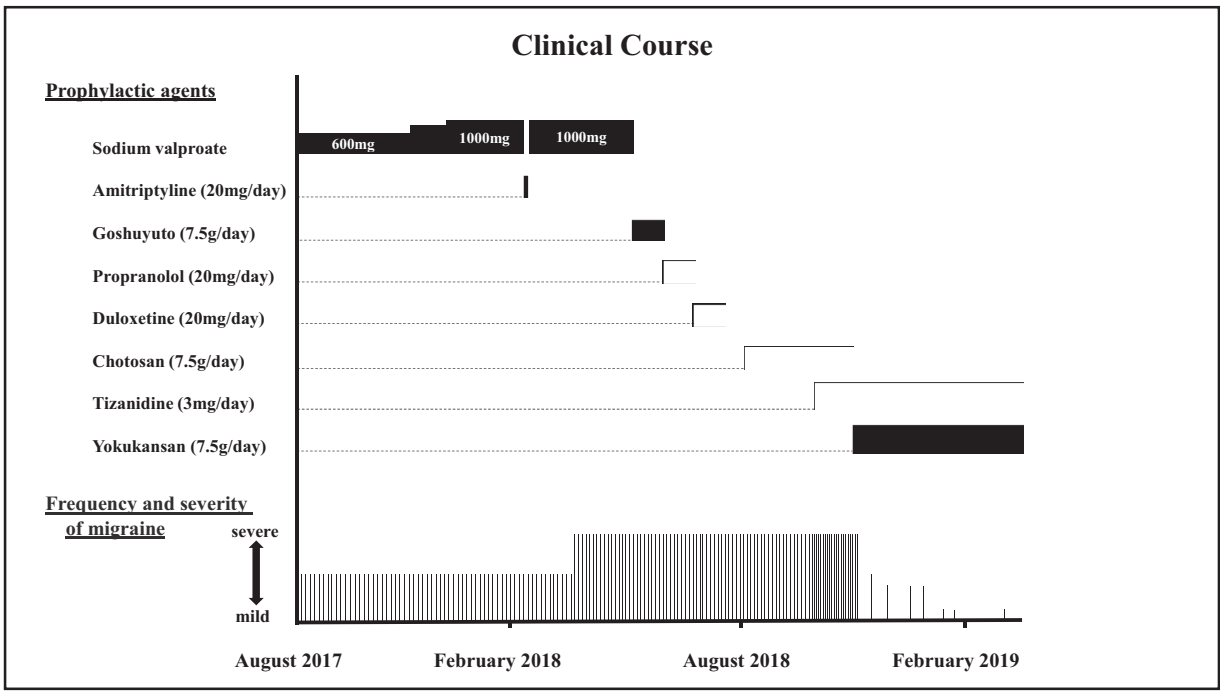

Figure 2. Clinical course. Migraine in this patient was refractory to a series of the following western and traditional Japanese Kampo medicines as prophylaxis: lomerizine hydrochloride, propranolol, sodium valproate, amitriptyline, duloxetine, Goshuyuto, and Chotosan. Her condition worsened severely such that she had no option but to take a leave of absence from work. Subsequent Yokukansan therapy markedly reduced the frequency and severity of chronic migraine, enabling a full return to work.

In April 2018, at age 39 years, management of the recurrent migraine episodes was unsuccessful. One day while at work, she developed a throbbing headache affecting the entire head. Oral sumatriptan (1 tablet) plus loxoprofen (1 tablet, 60 mg) was not effective, and she had to leave work early due to nausea, vomiting, and lightheadedness. She visited a nearby doctor, and returned home after some relief was achieved following drip infusion of an antiemetic and an analgesic. The headaches recurred similarly for 3 days, but were relieved with oral sumatriptan and loxoprofen. In the middle of May 2018, the sodium valproate (1000 mg/d) was deemed ineffective and was terminated. It was replaced by the traditional Japanese Kampo medicine Goshuyuto (7.5 g/d), which was started for prophylaxis. However, this was switched to propranolol (20 mg/d) after repeated episodes of severe headaches that required emergency transfer to the nearby clinic or a general hospital. However, she developed dizziness from the oral propranolol and the headaches still occurred every day for a month, and she could no longer work. Furthermore, oral or self-administered sumatriptan started to cause nausea, and consequently was terminated. The patient subsequently developed depressive symptoms, so duloxetine (20 mg/d) was started as a prophylactic, but she voluntarily stopped this immediately because of palpitations and teeth grinding. Oral Tramcet combined preparation (tramadol hydrochloride 37.5 mg plus acetaminophen 325 mg/tablet, 3 tablets/d) was started in July 2018, with relief of symptoms for 4 to 5 hours; this also was stopped because of drowsiness. The patient then had to take a 1-month leave of absence from work from August 2018. Trial therapy with oral Chotosan (a traditional Japanese Kampo, 7.5 g/d) was started during this period and moderately alleviated the headache, and she managed to make a partial return to work in September. She still needed to take oral sumatriptan every day, even though the pain relief was not adequate; at home, she could do nothing but lie down, and often had to leave work early or be absent from work frequently. Next, tizanidine (3 mg/d) was added as a precaution against tension-type headache. Chotosan was judged ineffective and switched to Yokukansan (7.5 g/d) in November. This switch led to a markedly reduced frequency of needing to leave work early, which decreased to 3 times per month with no full-day absences. There were no episodes of severe headache in December and the frequency also decreased to once per month in late December. As of this writing in June 2019, 6 months have elapsed since we prescribed Yokukansan at 7.5 g/d and the patient even forgets to take sumatriptan tablets to work because her condition is much improved with no signs of aggravation or recrudescence of headache.

3. Discussion

In this case, the patient was diagnosed as having migraine without aura based on ICHD-3, and was well managed with triptan preparations until childbirth. However, a hectic lifestyle with stress and fatigue from balancing work and childrearing caused increased frequency and severity of migraine. Several western medicines and traditional Japanese Kampo medicines (Goshuyuto and Chotosan) were administered as prophylaxis, but the chronic migraine was refractory to all such treatments. The patient had chronic migraine (≥15 headache days per month, of which at least 8 were migraine days), and this left her no option but to take a leave of absence from work. Fortunately, she had

some relief on taking the traditional Japanese Kampo medicine Yokukansan (TSUMURA Yokukansan extract granules), which markedly reduced the frequency and severity of headaches, enabling her full return to work. We consider this case relevant, even though it is a single case, because Yokukansan appeared to be an effective anti-migraine agent.

According to the survey in 1997 by Sakai et al, 8.4% (approximately 8.4 million) of individuals aged 15 years or older have migraines in Japan.[16] Migraines are characterized by severe unilateral throbbing headaches associated with nausea, vomiting, and hypersensitivity to light and sound, and often affect daily life (often patients are confined to bed). Given such severity, the use of prophylaxis is recommended if migraine episodes occur repeatedly or are prolonged (2 times or ≥6 days per month); the dose of nonsteroidal analgesics or triptan preparations is increased; or anxiety about having headaches restricts daily life.[1] In our case, the migraine was refractory to a series of the following agents: antihypertensive agents lomerizine hydrochloride (calcium channel blocker) and propranolol (beta-blocker); the antiepileptic agent sodium valproate; antidepressants amitriptyline and duloxetine, and traditional Japanese Kampo medicines Goshuyuto and Chotosan. When we tried Yokukansan, it markedly reduced the frequency and severity of migraines, enabling the patient's full return to work. Thus, we believe this case is of significance.

Yokukansan is a galenical preparation containing Atractylodes lancea rhizome (4.0 g), Poria sclerotium (4.0 g), Cnidium rhizome (3.0 g), Uncaria hook (3.0 g), Japanese Angelica root (3.0 g), Bupleurum root (2.0 g), and Glycyrrhiza (1.5 g) (Fig. 1). Indications include neurosis, insomnia, night crying, and irritability and/or agitation in infants. In adults, its efficacy for behavioral and psychological symptoms of dementia is well known.[15,17] It is not commonly used for treatment of headaches and has not yet been recommended in the Clinical Practice Guideline for Chronic Headache by the Japanese Headache Society 2013.[1] However, the efficacy of Yokukansan, as monotherapy and in combination with other antimigraine agents, was recently reported in the treatment of various types of headache, such as occipital neuralgia, migraine, and headaches caused by medication overuse in the treatment of depression.[8–14] We started Yokukansan based on the assumption that, given her natural drive, the patient did her very best to balance childrearing and work, which made her stressed and consequently worsened her condition resulting in chronic migraine.

The mechanism of migraine onset has not yet been elucidated, but the trigeminovascular theory is most likely involved.[18] More precisely, upon secretion of vasoactive substances following stimulation of the nerve terminals distributed in intracranial vessels, vasodilatation triggers sterile inflammation and inflammatory response then spreads through the vasculature. This excitation is transmitted to the brain and induces concomitant symptoms (eg, nausea and vomiting) and headache. It is highly likely that the neuropeptide serotonin, its receptors (particularly 5-$HT_{1B/1D}$ receptors widely distributed in cerebral vasculature), and the vasodilator calcitonin gene-related peptide are involved. Nevertheless, the mechanism of action of Yokukansan remains unclear, although the following actions have been reported: (1) suppression of neuronal excitation in the glutamatergic system through suppression of glutamate release action which affects N-methyl-D-aspartic acid receptors, activation of glutamate transporters, adjustment of glutamate uptake, and suppression of increases in the extracellular glutamate level[19–21]; (2) increased extracellular serotonin level in the serotonergic central nervous system through partial agonist effect on 5-HT_{1A} receptors and downregulation of 5-HT_{1A} receptors[22–24]; (3) inhibition of orexin A secretion[25]; and (4) anti-inflammatory effects.[26,27]

The interplay of these various actions of Yokukansan might have resulted in the marked prophylactic effect against migraine seen in our case.

Many traditional Japanese Kampo medicines, such as Keishininjinto, Kamishoyosan, Saikokeishito, Tokishigyakukagoshuyushokyoto, Goshakusan, Senkyuchachosan, Daisaikoto, Hangebyakujutsutemmato, Tokishakuyakusan, and Keishibukuryogan, have been reported to be effective for headache,[2–7] although they are not yet mentioned in the Clinical Practice Guideline for Chronic Headache.[1] These traditional Japanese Kampo medicines, including Yokukansan, are promising prophylactic agents for migraines that can be used globally. It is therefore desirable to conduct large-scale double-blinded placebo-controlled clinical studies at an early stage to confirm the prophylactic effect of therapy with traditional Japanese Kampo medicines.

Author contributions

Conceptualization: Hisanao Akiyama.
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Writing – original draft: Hisanao Akiyama.
Writing – review and editing: Hisanao Akiyama.
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